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Precancerous lesions in two counties of China with contrasting gastric cancer risk

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Background Gastric cancer (GC) is one of the most common cancers worldwide and shows remarkable geographical variation even within countries such as China. Linqu County in Shandong Province of northeast China has a GC rate that is 15 times higher than that of Cangshan County in Shandong, even though these counties are within 200 miles of each other.

Method In order to evaluate the frequency of precancerous gastric lesions in Linqu and Cangshan Counties we examined 3400 adults in Linqu County and 224 adults in Cangshan County. An endoscopic examination with four biopsies was performed in each individual of the two populations.

Results The prevalence of intestinal metaplasia (IM) and dysplasia (DYS) was 30% and 15.1%, respectively, in Linqu compared to 7.9% and 5.6% in Cangshan ($P < 0.01$). Within these histological categories, advanced grades were found more often in Linqu than in Cangshan. The prevalences of IM and DYS were more common at each biopsy site in Linqu, where the lesions also tended to affect multiple sites.

Conclusions The findings of this study support the concept that IM and DYS are closely correlated with risks of GC and represent late stages in the multistep process of gastric carcinogenesis.

Keywords Precancerous gastric lesions, gastric cancer, high and low risk, population

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Although gastric cancer (GC) mortality rates have been declining in most developed countries, GC is still the second leading form of cancer worldwide[1] and the most common cancer in China.[2] A survey of cancer mortality rates in China in 1990–1992 showed no decline in trend in GC mortality rates since an earlier survey in 1972–1975.[3] Gastric cancer mortality rates in China show remarkable regional variation.[2] For example, a 15-fold difference in GC rates has been found between Linqu and Cangshan counties in Shandong Province in northeast China.[2] Linqu County is a rural area with one of the highest GC mortality rates in the world ($70/10^5$ males and $25/10^5$ females per year). About 200 miles away, Cangshan County has similar ethnic, cultural, socioeconomic and rural features as Linqu, except that it is one of the leading agricultural producers of garlic. In Cangshan, GC mortality rates are only $5.0/10^5$ males and $3.0/10^5$ females per year, among the lowest in the world.[2]

According to Lauren's classification, there are two main types of GC, intestinal and diffuse.[4] Intestinal GC typically involves the distal stomach and predominates in areas where GC incidence rates are high.[5] The intestinal type appears to represent the final stage of a series of histopathological transformations over many years, with cancers arising from intestinal metaplasia (IM) and dysplasia (DYS).[5–8] The contrasting risks of GC in Linqu and Cangshan have provided an exceptional opportunity for studying the multistage process of GC carcinogenesis. To compare gastric histopathology in these high-risk and low-risk populations, an endoscopic survey was conducted in Linqu and Cangshan.

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Materials and Methods

The design of the endoscopic screening survey in Linqu is described in detail elsewhere.[7] In brief, after the names of all residents aged 35–64 had been transcribed from 14 village population rosters in Linqu County, health officials visited each person and offered a consent form inviting him or her to participate in GC screening in 1989 and 1990. All participants were given a brief physical examination, and their medical history was recorded. The subjects then received gastroscopy, with biopsies taken from seven standard sites in the stomach: four from the antrum, one from the angulus and one each from the lesser and greater curvatures of the body of the stomach.

From Cangshan County, a typical garlic farming area selected in 1994, one village was chosen at random for the present study. The same enrolment and endoscopic procedures used in Linqu were adopted in Cangshan, but only four biopsies were taken from the following gastric sites: one from the greater curvature of the body, one from the angulus and one each from the lesser and greater curvatures of the antrum.

Pathological diagnoses were based on criteria proposed by the Chinese Association of Gastric Cancer.[7] These criteria, along with photographs of superficial gastritis (SG), chronic atrophic gastritis (CAG), IM and DYS, are described in an earlier article.[7] Superficial gastritis is equivalent to non-atrophic gastritis and CAG is equivalent to multifocal atrophic gastritis (MAG) in international nomenclature.[8] Each slide was interpreted independently by three senior pathologists without knowledge of the area of origin of the slides, and double blind quality control samples of slides selected at random were reviewed by experts on gastric pathology in China and the US. Each biopsy was classified according to the presence or absence of SG, CAG, IM, DYS and GC. Each biopsy was given a diagnosis based on the most severe histology found in the biopsy, and each subject was assigned a diagnosis (hereafter referred to as the global diagnosis) based upon the most severe diagnosis among any of the biopsies.

Because the severity of gastric pathology is correlated with number of biopsies taken from the stomach, the global diagnoses in Linqu were based on the same four biopsy sites as in Cangshan, and differences between the two populations were assessed by χ^2 test for contingency tables.

Results

The endoscopic screening was completed on 3433 adults in 14 villages in Linqu (83% of the eligible population). A total of 36 subjects were later excluded because of insufficient tissue samples. Therefore, 3397 subjects were included in this analysis. Almost 90% of the participants were born in Linqu, and 96% were farmers or housewives.

The same examination was completed on 224 adults in one village in Cangshan (30% of the eligible population). More than 95% of the participants were garlic farmers or housewives and more than 95% of them were born in Cangshan. Ten subjects were excluded because of insufficient tissue samples, leaving 214 subjects for analysis of histopathology.

As shown in Table 1, the two populations were not significantly different with respect to age and sex distribution ($P > 0.05$). The prevalence of DYS was 15.1% in Linqu compared to 5.6% in Cangshan ($P < 0.01$). The prevalence of DYS was higher in males than females ($P < 0.01$) in Linqu but not in Cangshan. However, as there were only 12 cases of DYS in Cangshan, the confidence interval in the male-to-female odds ratio of DYS was 0.14 to 1.64. The DYS prevalence rates exhibited with an upward trend with age in Linqu. The prevalence of IM also was significantly higher in Linqu (30.1%) than Cangshan (7.9%). Age effects on IM were noted in both counties. Less than 1% of the subjects had normal gastric mucosa in Linqu compared to 8.9% in Cangshan ($P < 0.01$).

The coexistence of lesser conditions among those with DYS, IM or CAG as the most advanced lesion was also different between the two counties. Among 513 subjects with DYS in Linqu, 92.6% had associated deep IM (involving the deep pepsinogen secreting portion of gastric glands); however, among 12 subjects with DYS in Cangshan, 66.7% had associated deep IM ($P < 0.01$). Among subjects with IM as the most advanced lesion, 77.3% were graded as deep in Linqu compared to 58.6% in Cangshan. Among subjects with CAG, 43.4% were graded as severe in Linqu compared to 13.1% in Cangshan. In contrast, a higher proportion of hyperplasia of pits (foveolae) was found among subjects with CAG as the most advanced lesion in Cangshan (55.7%) compared with those in Linqu (10.7%) ($P < 0.01$).

Table 1 Age-specific prevalence of precancerous gastric lesions based on the global (most severe across four biopsies) diagnosis in Linqu and Cangshan

Subjects			DYS[a] (%)	IM[b] (%)	CAG[c] (%)	SG[d] (%)	Normal (%)
Linqu							
Age (years)	**n**	**%**					
35–39	1009	29.7	10.1	23.6	60.6	5.6	–
40–44	763	22.4	13.1	26.6	56.1	4.2	–
45–49	388	11.4	11.9	32.0	52.3	3.4	–
50–54	467	13.7	18.2	35.3	43.3	2.8	0.2
55–59	454	13.4	19.8	38.3	39.4	2.2	–
60–64	316	9.3	28.5	36.4	33.9	1.0	–
Total	3397	100.0	15.1	30.0	50.9	3.7	0.0
Sex							
Male	1789	52.7	18.4	29.4	48.2	3.7	–
Female	1608	47.3	11.4	30.4	54.0	3.8	0.0
Cangshan							
Age (years)	**n**	**%**					
35–39	49	22.9	2.0	2.0	77.6	12.2	6.1
40–44	42	19.6	9.5	–	71.4	14.3	4.8
45–49	26	12.1	–	7.7	69.2	11.5	11.5
50–54	29	13.6	–	23.3	63.3	3.3	10.0
55–59	28	13.1	14.3	3.6	60.7	7.1	14.3
60–64	40	18.7	7.5	15.4	64.1	2.6	10.3
Total	214	100.0	5.6	7.9	68.7	8.9	8.9
Sex							
Male	107	50.0	3.7	9.4	67.3	11.2	8.4
Female	107	50.0	7.5	6.5	70.1	6.5	9.4

[a] Dysplasia.
[b] Intestinal metaplasia.
[c] Chronic atrophic gastritis.
[d] Superficial gastritis.

Table 2 Prevalence of precancerous gastric lesions (based on most severe diagnosis within each biopsy) by biopsy site in Linqu and Cangshan

Site	DYS[a] (%)	IM[b] (%)	CAG[c] (%)	SG[d] (%)	Normal (%)
Linqu					
Body, greater curvature	1.1	5.7	26.1	55.7	11.3
Angulus	8.4	21.9	51.8	16.4	1.4
Antrum, lesser curvature	7.7	24.0	56.2	11.5	0.5
Antrum, greater curvature	3.8	15.4	59.5	20.3	0.8
Cangshan					
Body, greater curvature	0.5	–	12.7	40.6	45.7
Angulus	2.8	5.0	51.3	15.0	25.0
Antrum, lesser curvature	3.9	7.8	67.7	11.8	8.8
Antrum, greater curvature	2.8	4.0	63.6	12.5	17.0

[a] Dysplasia.

[b] Intestinal metaplasia.

[c] Chronic atrophic gastritis.

[d] Superficial gastritis.

We compared the extent of involvement of precursor lesions in the stomach. Among subjects with CAG, 52.5% of those in Linqu had this lesion in three or four biopsy sites compared to 18.4% in Cangshan ($P < 0.01$). For IM, 43% of those in Linqu had this lesion in two or more biopsy sites in Linqu compared to 11.8% in Cangshan ($P < 0.01$). For DYS, 25.4% of those in Linqu were detected with two or more sites compared to 16.7% in Cangshan ($P < 0.01$).

As shown in Table 2, the percentages of DYS, IM and CAG were higher in Linqu at each biopsy site, particularly in the angulus and lesser curvature of the antrum.

Discussion

In parallel with the widely varying risks of GC within Shandong Province, the prevalence rates of IM and DYS were nearly three to four times higher in Linqu County than in Cangshan County. For each diagnostic category, more advanced histological grades and more severe coexisting lesions were found in Linqu than in Cangshan. The two populations differed not only in the prevalence and severity of the gastric lesions, but also in the extensiveness of involvement. Dysplasia and IM were detected in multiple biopsy sites more frequently in Linqu than in Cangshan. Even for specific biopsy sites, the prevalences of DYS and IM were greater in Linqu than Cangshan. The concomitant variation in GC and precancerous lesions provides further evidence that IM and DYS represent late stages in the multistep process of gastric carcinogenesis.[6–14] In our prospective study of 3400 subjects with baseline histopathology in Linqu, we found that those with deep IM or DYS had a 30-fold greater risk of developing GC compared to those with CAG.[9] The small number with DYS make it difficult to assess those associations in Cangshan. The male-to-female ratio of GC mortality rates is 1:1.6 in Cangshan, however, diffuse type GC often predominates in a low risk area of GC[4,6] but we do not have the information on the histopathologic types of GC in Cangshan.

It is interesting that hyperplasia of gastric pits was nearly five times more prevalent among subjects with CAG in Cangshan than in Linqu. Gastric pit hyperplasia appears to reflect mucosal injury and repair during early stages of the inflammatory process leading to gastric atrophy.[12] Although CAG occurred often in Cangshan (82.2%), only about 10% of the diagnoses were graded as severe, compared to nearly 40% in Linqu. These data suggest that CAG is an early event in both areas, but that most subjects in Cangshan tend to remain in this stage, while progression to IM, DYS and GC is commonplace in Linqu. Our recent studies reveal that *Helicobacter pylori* infection is a major risk factor for the prevalence of CAG in Cangshan[15] while multiple risk factors, including *H. pylori* infection, are involved in the progression of precancerous lesions in Linqu.[16–18]

An intriguing possibility is that high garlic consumption in the Cangshan population retards the progression of gastric precursor lesions.[15] Cangshan has been well known for its garlic production for more than 1700 years. The residents consume an average of 20 g of fresh garlic per person per day compared to only 2.7 g in Linqu.[5,19]

Few epidemiological studies have compared the gastric histopathologies of populations at high and low GC risk. In Colombia, 56% of a selected population in a high-risk area had CAG compared to 13% in a low-risk area.[11] In a survey of Colombian migrants, those originating from the high-risk area had a much higher prevalence of IM (58.4%) compared to those from the low-risk area (19.1%).[12] Similarly, suction biopsies taken from population samples in nine provinces of China revealed a strong correlation between the prevalences of CAG and GC.[20] The present study provides further epidemiological evidence linking GC risks to the frequency and severity of precancerous lesions.

Some limitations of the present study should be mentioned. Because the GC rate is low in Cangshan, only 30% of the eligible population in the selected village in Cangshan consented to gastroscopic screening, indicating the potential for selection bias. However, those who participated had the same age, gender, education levels and socioeconomic status distribution as non-participants in the village in Cangshan as well as the subjects in Linqu County. Since subjects with gastric symptoms might be more willing to participate in the survey, the prevalences of DYS and IM reported for Cangshan may actually be overestimated. Thus, the true differences in precancerous gastric lesions between Linqu and Cangshan may be even greater than observed in our study.

In summary, although the present study has some limitations, this survey in the populations of two counties in Shandong with widely contrasting risks of GC revealed concomitant variation in the prevalence and severity of IM and DYS. Although CAG was common in Cangshan, the lesions tended to be less severe and associated with hyperplasia of gastric pits, when compared to the high-risk population in Linqu. Further studies in these populations may help identify factors that influence progression to more advanced gastric lesions, including the potential inhibitory effect of heavy garlic consumption in Cangshan.

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